Lymph node metastasis in thymic malignancies: A Chinese multicenter prospective observational study

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ABSTRACT

Objectives: To study the incidence and pattern of lymph node metastases in thymic malignancies.

Methods: This multicenter prospective observational trial with intentional lymph node dissection was carried out by the Chinese Alliance for Research in Thymomas (ChART). Data on patients with thymic tumors without pretreatment were collected prospectively. Results from this prospective study were then compared with those from a previously reported ChART retrospective study.

Results: Among 275 patients, metastasis was detected in 41 nodes (3.04%) in 15 patients (5.5%). The rate of lymph node metastasis was 2.1% (5/238) in patients with thymomas, 25% (6/24) in those with thymic carcinomas, and 50% (4/8) in those with neuroendocrine tumors ($P < .001$). The rate of lymph node metastasis in category T1 to T4 tumors was 2.7% (6/222) in T1, 7.7% (1/13) in T2, 18.4% (7/38) in T3, and 50% (1/2) in T4 ($P < .001$). Nodal involvement was significantly higher compared with the ChART retrospective study (5.5% vs 2.2%; $P = .002$), although the 2 groups were comparable in terms of tumor stage and histology. Metastasis was found in N1 nodes in 13 patients (86.7%) and in N2 nodes in 8 patients (53.3%); 6 patients (40%) had simultaneous N1/N2 diseases and 6 (40%) had multistation involvement. Based on World Health Organization histological classification and Union for International Cancer Control T category, patients were divided into a low-risk group (1/192; 0.5%) with T1-2 and type A-B2 diseases and a high-risk group (14/83; 16.9%) of category T3 and above or histology B3 and above tumors for nodal metastasis ($P < .001$). On multivariate analysis, type B3/thymic carcinoma/neuroendocrine tumors, category T3 or above, and N2 dissection predicted a greater likelihood of finding nodal metastasis.

Conclusions: Lymph node involvement in thymic malignancies is more common than previously recognized, especially in tumors with aggressive histology and advanced T category. Intentional lymph node dissection increases the detection of nodal involvement and improves accuracy of staging. In selected high-risk patients, systemic dissection of both N1 and N2 nodes should be considered for accurate tumor staging. (J Thorac Cardiovasc Surg 2018;156:824-33)

Central Message

Lymph node dissection should be considered in high-risk patients with high-grade tumors (World Health Organization type B3 thymoma, thymic carcinoma, and neuroendocrine thymic tumor) or local tumor extension (stage T3-4).

Perspective

Lymph node metastasis is a rare event in thymic tumors but is not uncommon in locally advanced or higher-grade tumors. According to Union for International Cancer Control T category and World Health Organization histology, patients can be divided into a low-risk group (0.5%) and a high-risk group (16.9%) of nodal metastasis. Intentional lymph node dissection helps improve the accuracy of staging. Systemic nodal dissection should be considered in high-risk patients.

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Abbreviations and Acronyms

ChART	= Chinese Alliance for Research in Thymomas
CI	= confidence interval
IASLC	= International Association for Studies in Lung Cancer
ITMIG	= International Thymic Malignancy Interest Group
NETT	= neuroendocrine thymic tumor
OR	= odds ratio
SEER	= Surveillance, Epidemiology, and End Results
VATS	= video-assisted thoracic surgery
WHO	= World Health Organization

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Thymic malignancies are relatively rare tumors compared with other malignant lesions of the chest.¹ Because of their rarity, many clinicopathological features of these tumors still await to be elucidated, including the pattern of lymph node involvement. Only in recent years have there appeared some reports on the incidence of lymph node metastasis in thymic malignancy, with a great discrepancy in the results.²⁻⁷ The Chinese Alliance for Research in Thymomas (ChART) recently published a retrospective study based on its multicenter database of 1617 patients.⁸ The overall metastasis rate of a mere 2.2% seems to suggest that nodal involvement is rather uncommon in this relatively indolent tumor, especially in low-grade, early-stage thymic tumors. However, nodal involvement is not uncommon in tumors of a higher stage or higher-grade histology, especially in neuroendocrine thymic tumors (NETTs). In addition, nodal involvement seems to denote worse prognosis, in addition to tumor invasion and histology, indicating its significance in predicting prognosis and directing treatment.

Along with the scarcity of knowledge on lymph node spread, neither lymph node dissection nor systemic sampling has ever been recommended as a standard practice for thymic tumors. The International Association for Studies in Lung Cancer (IASLC)/International Thymic Malignancy Interest Group (ITMIG) proposal for the Union for International Cancer Control staging system proposed a new lymph node map for thymic malignancy.⁹ Lymph

nodes located in the anterior mediastinum are defined as N1 nodes, and those in the deep mediastinum are defined as N2 nodes. If intentional lymphadenectomy were to be carried out in thymic tumors, there are no data indicating which subgroup of patients would be appropriate candidates or the extent to which lymph nodes should be harvested. Theoretically, in cases of total thymectomy, N1 nodes would have already been included in the resection area, but N2 nodes are usually left behind.

Based on these concerns, in the present study we aimed to further define the incidence and pattern of nodal metastases in thymic malignancies through intentional lymph node dissection/sampling.

PATIENTS AND METHODS

For this multicenter prospective observational study, Institutional Review Board approval was obtained from the participating hospitals, and written consent was acquired from all patients before surgery. Inclusion criteria were patients age from 15 to 80 years with an anterior mediastinal lesion clinically suspicious for thymic tumor and considered operable by the surgeon. Exclusion criteria were patients who had received any preoperative induction therapy for advanced tumors or those medically unfit for surgery. We deliberately excluded patients with preoperative therapies, because effective induction might downstage the tumor and lead to underestimation of the actual incidence of nodal metastasis. Patients who turned out to have a lesion other than thymic malignancy were then eliminated from the study.

All patients were operated on with an intention to cure. Thymectomy, instead of thymomectomy or tumor enucleation, was the standard procedure. In patients with myasthenia gravis, extended thymectomy was performed. The surgical approach (open or minimally invasive, median or lateral incision) was chosen according to the surgeon's preference without any special requirement for lymph node dissection, except that transcervical incision was considered unacceptable for nodal retrieval. The minimal request for this study was that at least 1 anterior mediastinal lymph node station close to the primary lesion be intentionally harvested and sent for histological examination (Video 1). However, there was no definite requirement as to the number or extent (unilateral or bilateral, N1 or N2, according to the IASLC/ITMIG definition) of lymph node dissection

VIDEO 1. Lymph node sampling via a bilateral video-assisted thoracic surgery approach. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31034-1/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31034-1/fulltext).

or sampling, although surgeons were encouraged to harvest as many nodes as possible.

Laterality, local extension, and histology subtype of the primary tumor were documented to study the relationships between different tumors and patterns of lymph node involvement. Tumors with their epicenter lateral to the internal mammary vessels on one side on preoperative computed tomography scan were considered laterally located, whereas tumors with their epicenter between the bilateral internal mammary vessels were considered centrally located. Tumor staging was based on the IASLC/ITMIG proposal for the Union for International Cancer Control staging system.¹⁰ Tumor histology was classified according to World Health Organization (WHO) type,¹¹ with NETT considered an individual subgroup. Results from this prospective study were then compared with those from a previously reported ChART retrospective database study.⁸

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, Ill). Categorical variables were analyzed using the χ^2 test, or the Fisher exact test for small samples, for differences between the groups. Continuous data were compared using the Student *t* test. To identify potential risk factors predicting nodal involvement, univariate binary logistic regression was performed, followed by a multivariable analysis including only variables with $P < .10$ in the univariate analysis. Statistical significance was accepted as $P < .05$ throughout the study.

Nomogram Construction

We generated a predictive nomogram model to predict high-risk patients. Then, based on the results of the multivariable analysis, variables that achieved significance at $P < .05$ were selected to formulate a nomogram using R 3.4.1 (<http://www.r-project.org>) with the rms package.

RESULTS

A total of 275 patients with thymic tumors who underwent surgical resection at 15 tertiary referral centers in the ChART group between June 1, 2014, and August 31, 2016, were entered into the study. The cohort included 130 males (47.3%) and 145 females (52.7%), with a mean age of 53.9 years (range, 18-80 years). Fifty-six patients (20.4%) had a concomitant autoimmune disease, the vast majority with myasthenia gravis ($n = 52$). The patients had a total of 243 thymomas (88.4%), 24 thymic carcinomas (8.7%), and 8 NETTs (2.9%). Surgical approaches included 134 open procedures (48.4%) and 141 video-assisted thoracic surgery (VATS) resections (51.3%). Bilateral lymph nodal dissection/sampling was carried out in 11.8% (16/135) of patients undergoing open surgery and in 5% (7/141) of those undergoing a VATS procedure. No surgical mortality or major complications directly related to lymph node harvesting were recorded during the study. Complete resection was confirmed by postoperative histological examination in 268 cases (97.5%). Pathological T1a, T1b, T2, T3, and T4 tumors were identified in 198 (72%), 24 (8.7%), 13 (4.7%), 38 (13.8%), and 2 (0.7%) patients, respectively.

A total of 1347 lymph nodes from 847 stations were harvested, with a mean number of 4.9 nodes and 3.1 stations per patient (Figure 1). Patients undergoing VATS surgery

actually had a greater number of lymph nodes (5.31 vs 4.46; $P = .05$) and more stations (3.30 vs 2.84; $P = .017$) harvested, and more N2 dissections (1.57 vs 1.45; $P = .048$) compared with patients undergoing open procedures. On histological examination, nodal metastasis was detected in 41 nodes (3.04%) in 15 patients (5.5%). Demographic characteristics, surgical approaches, and extent of nodal retrieval in patients with or without nodal disease are presented in Table 1. Overall, the nodal metastasis rate was significantly higher than the 2.2% rate (35/1617; $P = .002$) reported in the retrospective ChART study,⁸ although no significant difference in the percentage of histological subtypes ($P = .102$) or T categories ($P = .188$) was detected between the retrospective and prospective databases (data not shown). Compared with the results of the retrospective study, nodal involvement was much more common in most histology types and T categories in stratified analysis (Table 2). The overall metastasis rate was 2.1%, in thymomas, 25% in thymic carcinomas, and 50% in NETTs ($P < .05$), and 2.0% in T1a tumors, 8.3% in T1b tumors, 7.7% in T2 tumors, 18.4% in T3 tumors, and 50% in T4 tumors ($P < .001$). No lymph node involvement was found in type A or B1 thymomas. Stations of lymph nodes harvested and lymph node dissection rates are listed in Table 3. No significant difference in lymph node dissection rate was detected between N1 and N2 nodes (3.1% vs 2.7%; $P = .743$).

In univariate analysis, WHO histology, T category, tumor size, and bilateral and N2 node sampling were significantly associated with positive nodal disease. In multivariate analysis, WHO type B3/thymic carcinoma/NETT ($P = .001$; odds ratio [OR], 9.857; 95% confidence interval [CI], 2.522-38.521), category T3-4 ($P = .009$; OR, 2.281; 95% CI, 1.229-4.23), and N2 node dissection ($P = .015$; OR, 5.96; 95% CI, 1.418-25.05) independently predicted a greater likelihood of finding nodal metastases (Table 4). Based on these 3 factors, a nomogram predicting nodal involvement was built (Figure 2), which calculates the risk of nodal disease as follows:

$$\text{LN(Risk)} = -5.738 + 1.649T + 2.288 \text{ WHO} + 1.785 \text{ N1/2}.$$

According to histology and T category alone, patients could be divided into a low-risk group, with stage T1-2 and type A/AB/B1/B2 thymomas, and a high-risk group, with stage T3 and above or higher-grade histology (B3 thymoma, thymic carcinoma, NETT). N2 node dissection was carried out in 44.3% (85/192) of patients in the low-risk group and in 36.1% (30/83) of patients in the high-risk group ($P = .210$). The low-risk group accounted for 69.8% (192/275) of the study population, with lymph node involvement seen in only 1 patient (0.5%) with a giant type AB tumor. In contrast, nodal metastasis was 16.9% (14/83) in the high-risk group, which

FIGURE 1. Numbers of nodes and stations of nodes harvested per patient. A, Numbers of nodes harvested per patient. B, Numbers of stations of nodes harvested per patient.

TABLE 1. Demographic characteristics of the patients, surgical approaches, and extent of tumor resection

Characteristic	N(–) (n = 260)	N(+) (n = 15)	P value
Age, y, mean ± SD	53.85 ± 11.8	53.87 ± 9.9	.349
Sex, n (%)			
Male	124 (95.4)	6 (4.6)	.562
Female	136 (93.8)	9 (6.2)	
Tumor size, cm, mean ± SD	5.57 ± 2.65	7.5 ± 4.03	.005
Preoperative autoimmune disease, n (%)	54 (96.4)	2 (3.6)	.743
Surgical approach, n (%)			
Open	129 (91.8)	11 (8.2)	.063
VATS	137 (97.2)	4 (2.8)	
T category, n (%)			<.001
T1a	194 (98)	4 (2.0)	
T1b	22 (91.7)	2 (8.3)	
T2	12 (92.3)	1 (7.7)	
T3	31 (83.8)	7 (18.4)	
T4	1 (50)	1 (50)	
WHO histology type, n (%)			<.001
A-B2	204 (98.6)	3 (1.4)	
B3	34 (94.4)	2 (5.6)	
Carcinoma	18 (75)	6 (25)	
NETT	4 (50)	4 (50)	
LN dissection, n (%)			
Unilateral	158 (97.5)	4 (2.5)	.013
Bilateral	102 (90.3)	11 (9.7)	
N1 only	131 (97.8)	3 (2.2)	.022
N1 + N2	129 (91.5)	12 (8.5)	

N(–), Without nodal involvement; N(+), with nodal metastasis; SD, standard deviation; VATS, video-assisted thoracic surgery; WHO, World Health Organization; NETT, neuroendocrine thymic tumor; LN, lymph node.

accounted for only 30.2% (83/275) of all patients enrolled in this study, significantly more common than in the low-risk group ($P < .001$).

Among the 15 patients with nodal diseases, metastasis was found in N1 nodes in 13 patients (86.7%) and in N2 nodes in 8 patients (53.3%). Six of these 15 patients (40%) had simultaneous N1/N2 disease, and 6 (40%) had multi-station involvement (Table 5). Broken down by tumor stage and histology, only 1 of 207 patients (0.5%) with a type A-B2 tumor had N2 involvement, compared with 3 of 43 patients (6.9%) with a T1-2 tumor and 4 of 25 (16%) with a T3-4 type B3/C/NETT tumor. Three of the 15 patients (20%) had bilateral nodal metastasis, all with NETTs (atypical carcinoid), and all had simultaneous N1/N2 diseases. Of the 5 patients with unilateral N2 involvement, 4 had a laterally located tumor, and all 4 had node involvement on the ipsilateral side of the primary tumor. In 1 patient with unilateral N2 involvement, the tumor was a centrally located squamous cell carcinoma invading into bilateral lung. When N2 node dissection was planned, the risk of

TABLE 2. Comparison of lymph node metastasis rates in different histology types and T categories between the ChART retrospective and prospective studies

Variable	Nodal metastasis, n/N (%)		P value
	ChART retrospective	ChART prospective	
WHO histology			
A	0/98 (0)	0/21 (0)	–
AB	0/424 (0)	2/83 (2.4)	.025
Micronodular	0/2 (0)	0/6 (0)	–
B1	0/245 (0)	0/36 (0)	–
B2	1/275 (0.4)	1/61 (1.6)	.358
B3	6/266 (2.3)	2/36 (5.6)	.244
Ca	21/265 (7.9)	6/24 (25)	.006
NETT	7/42 (16.7)	4/8 (50)	.037
T category			
T1a	3/1124 (0.3)	4/198 (2.0)	.002
T1b	0/99 (0)	2/24 (8.3)	.037
T2	5/72 (6.9)	1/13 (7.7)	.923
T3	25/295 (8.5)	7/38 (18.4)	.050
T4	2/27 (7.4)	1/2 (50)	.056

ChART, Chinese Alliance for Research in Thymomas; WHO, World Health Organization; Ca, thymic carcinoma; NETT, neuroendocrine thymic tumor.

revealing N2 nodal metastasis according to the nomogram was 0.019 for WHO type A-B2 and category T1-2 tumors, 0.099 for type A-B2 and T3-4 tumors, 0.189 for type B3-NETT and T1-2 tumors, and 0.984 for type B3-NETT and T3-4 tumors.

DISCUSSION

In this multicenter prospective observational study with intentional lymph node retrieval during total thymectomy, we detected a significantly higher incidence of lymph node involvement than in the previously reported ChART retrospective study.⁸ N2 node dissection, along with higher-grade tumor histology and advanced T category, were found to be associated with increased nodal-positive rate. Patients with thymic tumors could be divided into high-risk and low-risk subgroups depending on tumor histology and T category, suggesting that selective dissection may be warranted.

Lymph node dissection for malignant tumors is performed to increase the accuracy of tumor staging, to ensure radical removal of the disease, and to improve surgical outcomes. However, intentional lymph node dissection or sampling is seldom recommended as a routine procedure for thymic malignancies. In this study, the overall rate of lymph node involvement of 5.5% (15/275) is more than double the 2.2% rate (35/1617; $P = .002$) in a previously reported retrospective analysis of the same study group without lymph node dissection.⁸ Although there was no significant difference in histological subtype or T category distribution between the retrospective and prospective databases, we

TABLE 3. Stations of lymph nodes dissected/sampled and rate of nodal involvement at each station

Node station	IASLC level	ITMIG map	LN's harvested, n (%)	LN dissection rate, n (%) [*]
Prevascular	3a	N1	239 (86.9)	5 (2.1)
Upper paratracheal	2	N2	94 (34.2)	3 (3.7)
Lower paratracheal	4	N2	94 (34.2)	1 (1.1)
Right hilum	R10	N2	50 (18.2)	1 (2)
Para-aortic	6	N1	219 (79.6)	9 (4.1)
Subaortic	5	N2	100 (36.3)	4 (4)
Left hilum	L10	N2	36 (13.1)	1 (2.8)

IASLC, International Association for Studies in Lung Cancer; ITMIG, International Thymic Malignancy Interest Group; LN, lymph node. ^{*}Lymph node dissection rate at each station = number of patients with nodal metastasis/number of patients with nodes harvested at that station.

compared the rates of nodal metastasis in each WHO histology type and T category between the 2 cohorts to further exclude potential selection biases. No lymph node involvement was found in type A or B1 tumors in either study. Compared with the ChART retrospective study, the rate of nodal metastasis was much higher for all other histology types and each T category in the prospective study. The differences between the 2 cohorts were statistically significant except for type B2 and B3 and category T2 tumors, likely because of the small number of total and node-positive cases. This clearly indicates that intentional lymph node retrieval would increase the yield of detection of nodal diseases in thymic tumors, and thus is at least important for accurate staging and radical removal of the disease.

In the present study, lymph node metastasis was seen in 2.1% of patients with thymomas, in 25% of those with thymic carcinomas, and in 50% of those with NETTs. The highest rates of lymph node involvement reported to date were from 2 retrospective studies using the Surveillance, Epidemiology, and End Results (SEER) database,^{5,6} although accurate comparisons among different studies are

difficult. In a study including only patients with at least 1 lymph node harvested for histological examination, Weksler and colleagues⁵ reported rates of lymph node spread of 33.5% in thymic carcinomas and 62.3% in NETTs, similar to our results. In another study reported by the same authors, the rate of nodal metastasis was surprisingly high in thymomas (13.3%).⁶ However, more than one-half of the tumors in their cohort were Masaoka stage >III, whereas >85% of the tumors in our series were in category T1-2, which corresponds to Masaoka stage I-II. This discrepancy is understandable, because the SEER database is basically a cancer registry. Moreover, our understanding of thymic malignancy has changed significantly, and all thymic tumors are now considered malignant in nature.¹² Thus, cases recorded in the SEER database might not represent the general picture of these tumors. In fact, the higher rate of nodal involvement in the series of Weksler and colleagues also supports our finding that increased nodal involvement is associated not only with tumor histology, but also with the extent of local invasion of the primary lesion. Both

TABLE 4. Univariate and multivariate analysis for potential risk factors predicting lymph node involvement in thymic tumors

Variable	OR (95% CI)	P value
Univariate analysis		
Age	1.000 (0.956-1.046)	.997
Sex, male vs female	0.731 (0.253-2.113)	.563
Tumor size	1.236 (1.049-1.455)	.011
Preoperative autoimmune disease, no vs yes	1.704 (0.373-7.779)	.492
WHO histology, B3-C vs A-B2	14.571 (3.974-53.427)	<.001
T category, T3-4 vs T1-2	8.143 (2.766-23.972)	<.001
Surgical approach, open vs VATS	3.111 (0.965-10.023)	.057
LN dissection (bilateral vs unilateral)	4.26 (1.321-13.741)	.015
LN dissection (N1 + N2 vs N1 only)	4.062 (1.12-14.731)	.033
Multivariate analysis		
WHO histology type (B3-C vs A-B2)	9.857 (2.522-38.521)	.001
T category (T3-4 vs T1-2)	2.281 (1.229-4.23)	.009
LN dissection (N1+ N2 vs N1 only)	5.96 (1.418-25.05)	.015

OR, Odds ratio; CI, confidence interval; WHO, World Health Organization; LN, lymph node.

FIGURE 2. A nomogram predicting detection of positive nodal status in thymic tumor patients. *UICC*, Union for International Cancer Control; *WHO*, World Health Organization; *Ca*, thymic carcinomas; *NETT*, neuroendocrine thymic tumors.

factors should be considered when predicting the likelihood of lymphatic spread in these patients.

According to our results, the risk of lymph node metastasis was not associated with patient age or sex or the presence of autoimmune disease. Tumor size differed between patients with nodal disease and those without nodal disease in univariate analysis but not in multivariate analysis. Apart from N2 dissection, only tumor histology and T category were independent predictors for nodal involvement. This finding is in accordance with our previous study using the ChART retrospective database.⁸ Based on these results, patients could be divided into a low-risk group with nodal metastasis and a high-risk group with tumors with local invasion into the neighboring organs (stage T3 and above) or with higher-grade histology (B3 thymoma, thymic carcinoma, or NETT). Only 1 patient (0.5%) in the low-risk group (69.8% of the study population) had nodal disease, whereas 16.9% of the high-risk patients (30.2% of the study population) already had lymph node metastasis. If intentional lymphadenectomy were carried out selectively only in the high-risk group, nearly 70% of the patients with thymic tumors could be exempted from unnecessary dissection. It is also noteworthy that the frequency of N2 node dissection was similar in these 2 groups; therefore, it is unlikely that the extent of dissection accounted for the different rates of nodal involvement in these patients.

Another important point when considering lymph node evaluation is the extent of nodal dissection. Among different regions there seems to be a preference of surgical approaches for thymic tumors (VATS vs open; median vs unilateral).¹³ Whether this would have any impact on lymph

node retrieval is unknown. In this study, we did not find any significant association between surgical approach and lymph node yield. This result is highly relevant to the choice of surgical procedure, with minimally invasive surgery increasingly used for thymic tumors,¹⁴ with a unilateral approach in the majority of these procedures. Although most tumors selected for VATS or robot-assisted surgery are early-stage lesions that would fall into our low-risk group, the rate of nodal involvement was still 2.7% in T1 tumors and 7.7% in T2 tumors. It is noteworthy that all the patients in this study underwent total thymectomy, including those who underwent tumors resection by VATS. Theoretically, N1 nodes, located in the anterior mediastinum, would have already been removed before the entire thymus was resected via total thymectomy.

N2 node harvesting is even less often included in surgical resection of thymic tumors, unless performed intentionally. Whether it is indeed necessary is never known. In this study, the rates of N1 (4.7%) and N2 (2.9%) metastasis seemed to be similar, and 40% of the patients with nodal involvement had simultaneous N1/N2 disease. In addition, we found that the lymph node dissection rate, defined as the number of patients with nodal metastasis divided by the number of patients with that node station harvested, was similar between the N1 region (3.1%) and N2 region (2.7%; $P = .743$). Moreover, N2 dissection turned out to be another independent predictive factor for nodal disease. This would suggest that once lymph node metastasis occurs in thymic tumors, it tends to be multistational and often involves both N1 and N2 nodes. If lymph node dissection is deemed necessary, both N1 and N2 nodes should be harvested to

TABLE 5. Clinical characteristics of 15 patients with lymph node metastasis

Patient	WHO histology	Clinical stage	Surgical approach	Tumor size, cm	Pathological stage	Extent of lymphadenectomy	Location of positive LNs (IASLC level)
1	AB	T3N0M0	Open	9 × 9 × 5	T3N1M0	N2	L6
2	AB	T3N0M0	Open	15 × 11 × 8	T1aN2M0	N2	R10
3	B2	T3N0M1a	Open	8.5 × 5 × 3	T3N1M1a	N1	L6
4	B3	T3N0M0	Open	4 × 5 × 4	T4N2M1a	N2	L6, L5
5	B3	T1N0M0	VATS	4 × 3 × 2.5	T1aN2M0	N2	L5
6	Ca	T1bN0M0	Open	7 × 5 × 4	T3N1M0	N2	L6
7	Ca	T1aN0M0	VATS	4 × 2 × 3	T1aN2M0	N2	L6, L5
8	Ca	T3N0M0	Open	7 × 4.5 × 4	T3N1M0	N1	R3a
9	Ca	T3N0M1a	Open	4 × 3 × 2	T2N1M1a	N2	L6
10	Ca	T3N0M0	Open	5 × 4.5 × 3.6	T3N1M1a	N1	R3a
11	Ca	T4N2M0	Open	13 × 10 × 5	T3N2M0	N2	L6, L5
12	NETT	T2N0M0	VATS	4.5 × 3.5 × 3	T1bN1M0	N2	R3a
13	NETT	T3N0M0	Open	9.5 × 8 × 4	T3N2M0	N2	R2, R3a, L5
14	NETT	T1N0M0	Open	15 × 8.5 × 8	T1aN2M0	N2	L6, L10, R2
15	NETT	T1bN0M0	Open	5 × 4 × 4	T1bN2M0	N2	R2, R3a, R4, L6

WHO, World Health Organization; LN, lymph node; IASLC, International Association for Studies in Lung Cancer; VATS, video-assisted thoracic surgery; Ca, thymic carcinoma; NETT, neuroendocrine thymic tumor.

ensure complete resection and accurate staging. This should apply only to a selected group of high-risk patients, however. According to the nomogram that we built to predict nodal involvement, the risk of revealing N2 nodal metastasis would be only 0.019 for WHO type A-B2 and category T1-2 tumors, but 0.984 for type B3-NETT and T3-4 tumors.

Our results also showed that N2 involvement was usually on the ipsilateral side of tumor extension, except for NETTs. This seems to suggest that for thymomas and thymic carcinomas, only N2 nodes on the side of tumor invasion need to be retrieved. According to our results, at least stations 2 and 4 on the right side or station 5 on the left side, depending on the laterality of the primary lesion, should be harvested if N2 dissection is considered necessary. Hilar nodes on the ipsilateral side of the tumor should be included as well. The fact that bilateral dissection did not turn out to be an independent risk factor in multivariate analysis for nodal disease also supports this idea. In fact, all 3 patients with bilateral nodal involvement had NETT (atypical thymic carcinoid) and simultaneous N1/N2 metastasis, and 2 of them had bilateral N2 disease. Given that in both the prospective and retrospective studies, patients with NETT had the highest rate of lymph node involvement, special attention should be given to more extensive lymph node dissection in this group of patients. Because biopsy is usually not recommended for upfront surgery in patients with thymic malignancy, intraoperative frozen sections may be used to determine tumor histology and the extent of nodal dissection onsite.

One limitation of this study is the relatively small number of patients with thymic carcinoma and NETT. Nonetheless, nodal metastasis was found to be significantly higher in these subtypes, and both thymic carcinoma and NETT were identified as important risk factors for predicting nodal status. In addition, our study did not specify the extent of lymph node harvesting during thymectomy, and one-half of the patients did not have N2 nodal dissection. This would certainly limit our ability to more precisely define the pattern of lymph node involvement. Moreover, the small number of cases with nodal metastasis also might affect the accuracy of risk factor analysis. However, this is the sole prospective study with intentional lymph node retrieval in thymic tumors. In contrast to all other retrospective studies on the same topic, we managed to accrue a large patient cohort in a very limited study period. This also helped put the risk of confounding bias caused by evolution in surgical techniques to a minimum.

In conclusion, we found a significantly increased rate of lymph node metastasis in thymic tumors after intentional lymph node dissection/sampling. Once nodal metastasis occurred, it was often multistational, involving both N1 and N2. Our results suggest that lymph node dissection should be recommended in high-risk patients with high-grade tumors (WHO type B3 thymoma, thymic carcinoma, and NETT) or local extension (category T3-4). In addition to total thymectomy for N1 nodes, N2 nodes, especially those on the ipsilateral side of tumor extension, should be harvested as well. Bilateral

dissection is usually unnecessary, except for the rare cases of neuroendocrine tumors with a high prevalence of extensive nodal involvement. These factors should be taken into consideration when designing surgical procedures for thymic malignancy.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/17AM/2017-05-03/RM312/05-03-17_Room312_0926_Fang.mp4.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: thymic malignancy, surgery, lymph node metastasis, lymph node dissection

Discussion

Dr Cameron D. Wright (Boston, Mass). Thank you, Dr Fang, for a very well-presented study that is somewhat provocative, and for providing me with the manuscript. I have two questions. It appears there was some selection bias in dissecting the deep mediastinal nodes, in that those were

clearly the worst tumors. Did you have an idea beforehand of the histology or intraoperatively did you find out what the histology was in making that decision between an N1 versus an N2 nodal dissection?

Dr Wentao Fang (Shanghai, China). Thank you. I think it is a very good question. Actually, there was no requirement as to the extent or number of lymph node dissections in this protocol, but we did look into the rate of N2 deep mediastinal dissection in patients with low risk and high risk, and we found a less than 8% difference between the two groups. Of course, this was not statistically significant, so there is no difference.

Dr Wright. The second question is, moving on, where do we take this study? How do we set it in the context of taking care of our thymic tumor patients? I take your point that we ought to consider dissection for T3, T4, and bad histology lesions with a 15% to 20% rate of positive lymph nodes, but what do we do then? I doubt that there is going to be much difference in survival, but importantly right now the standard of care is not to give chemotherapy, but what about giving chemotherapy to these patients?

Dr Fang. I think this is highly relevant to clinical practice. Unfortunately, there is no good evidence that supports postoperative chemotherapy. We do have a protocol at our hospital that would give adjuvant chemotherapy to all patients with lymph node metastasis; however, this is more of an intuitive decision. The Chinese Alliance for Research in Thymomas has also published a retrospective study on the effect of adjuvant chemotherapy for advanced-stage

thymic tumors; however, even after propensity score matching, we didn't find any beneficial effect of adjuvant chemotherapy. So we really don't know the answer yet.

Dr Hiroshi Date (*Kyoto, Japan*). Vincent, that was an excellent presentation. I would like to know if you have PET scan data before surgery, and if it could pick up the patient with lymph node metastasis?

Dr Fang. That's a good question. At Shanghai Chest, we offer PET scan or nuclear scan for all thymic tumor patients, but it is not a routine practice among all the institutions in this study, because PET scan, as you know, is not covered by insurance in China, and in my experience, its sensitivity of detecting lymph node metastasis in thymic tumors is quite low. It's not that good except for neuroendocrine tumors, which tend to have quite extensive disease involvement.

Dr Scott Swanson (*Boston, Mass*). I enjoyed your paper. It was a great presentation. You may have said this, but I missed it. Do you know how the people with lymph node-positive disease failed? Did they fail locally, distantly? What happened to those patients?

Dr Fang. Thanks for the question. I don't have the exact number, but in my impression, most patients with neuroendocrine tumors tend to have lymph node metastasis and finally distant metastasis; lymph node metastasis always comes first.

Dr Swanson. Do they fail in the chest?

Dr Fang. Most of them would be in the neck.

Dr Swanson. Should they get radiation?

Dr Fang. That's our practice, but I don't know whether if there is any evidence to support that. It is more palliative.

APPENDIX E1. MEMBERS OF CHINESE ALLIANCE FOR RESEARCH IN THYMOMAS (ChART)

Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, and Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen and Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen and Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui and Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang and Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, and Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen and Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang and Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu and Qing Lin, Jiangxi

People's Hospital, Nanchang, China; Yongyu Liu and Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu and Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu and Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu and Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang and Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang and Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou and Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.